ADDITION OF β -CHLOROETHYLSULFENYL CHLORIDE TO DIMETHYLACRYLIC ACID DERIVATIVES

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UDC 542.955:547.431.6+547.39

It was established that insertion of the moiety of a nitrogen mustard molecule into an amino acid or a peptide lowers its toxicity and increases the selectivity of its action on tumors. Analogous derivatives of a sulfur mustard have received little study up to now [1]. The present investigation is devoted to the addition of $ClSCH_2CH_2Cl$ to dimethylacrylic acid derivatives in order to obtain physiologically active compounds.

 β -Chloroethyl sulfenyl chloride was added to dimethyl acrylic acid derivatives in absolute chloroform solution at -8°C.



 $R = CH(COOCH_3)CH_2C_6H_5 (a); CH (CONH_2)CH_2C_6H_5 (b); CH(COOH)CH_2C_6H_5 (c); p-C_6H_4COOC_2H_5 (d); p-C_6H_4COOCH_3 (e)$

For dimethylacrylic acid the adducts are thermodynamically stable, as was shown by our previous studies on the addition of methylsulfenyl chloride [2].

The starting amides needed for the synthesis were synthesized by the conventional acylation of the corresponding amino acid esters with the acid chloride of dimethylacrylic acid.

 $\begin{array}{c|c} H_{3}C & \xrightarrow{2RCH (NH_{2}) COOR_{1}} & H_{3}C \\ H_{3}C & \xrightarrow{RCH (NH_{2}) COOR_{1}} & H_{3}C \\ \hline & & & & \\ H_{3}C & \xrightarrow{RCH (NH_{2}) COOR_{1}} & H_{3}C \\ \hline & & & & \\ \hline & & & & \\ (I) & & & \\ COOR_{1} \\ \hline \end{array}$

Good yields of (I) were obtained in this way by the reaction of the methyl esters of amino acids (2 moles), or of the amino acid ester hydrochlorides, in the presence of triethylamine (2 moles) with the acid chloride of dimethylacrylic acid. When the order of addition was reversed, the reaction of the acid chloride of dimethylacrylic acid with a mixture of anesthesine (benzocaine) and triethylamine gave a mixture of anestheside (Id) and the anestheside of β -methylvinylacetic acid (III) in a ratio of 30 and 70% respectively (NMR spectroscopy).



The saponification of (Ia) with alkali in methanol gave (Ic), while its reaction with aqueous ammonia smoothly gave the amide (Ib).

Institute of Biochemistry, Academy of Sciences of the Lithuanian SSR, and the Institute of Heteroorganic Compounds, Academy of Sciences of the USSR. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 10, pp. 2271-2275, October, 1971. Original article submitted March 6, 1970.

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	(IIa — e)
UUNUJ HJ	-cn-comm SCH2CH2CH2CI
H _s C	H _s C
	-
	TABLE

Com-		-		The second s		EL:	ound, 9/				Calc	ulated	20	
punod	R	Yield,%	Mp, °C (solvent)	Empirical formula	υ	щ	5	z	s	υ	H	ច	z	ø
cī.	CH (COOCH ₃) CH ₂ C ₆ H ₅	92	82-83 (ethyl acetate and petrole- um ether)	C17H23Cl2NO ₃ S	51,81	5,95	17,97	3,11	8,32	52,04	5,90	18,07	3,57	8,17
م.	CHCII2C6H5	82	(ethyl acetate and petrole- um ether)	C16H22Cl2N2O2S	51,07	5,88	18,72	7,45	7,72	50,93	5,88	18,79	7,42	8,49
υ	CH ₂ C ₆ H ₅ CH (COOH)	60	(ethyl acetate and hexane)	$\mathrm{C}_{\mathrm{j6}}\mathrm{H}_{21}\mathrm{Cl}_2\mathrm{NO}_3\mathrm{S}$	50,59	5,58	18,82	3,72	77,77	50,79	5,59	18,74	3,70	8,47
ą	<i>p</i> -C ₆ H ₄ COOC ₂ H ₅	95	112113 (ether and hexane)	$C_{16}H_{a1}Cl_2NO_3S$	51,33	5,75	17,82	3,82	8,25	50,79	5,59	18,74	3,70	8,47
e	p-C ₆ H ₄ COOCH ₈	94	107108 (ether)	C ₁₅ H ₁₉ Cl ₂ NO ₃ S	49,76	5,31	18,91	4,01	8,67	49,46	5,25	19,46	3,84	8,80

TABLE 2. Hac CCH-CONHR (IV a-c)

	CI	SO2CH2CI	1 ₂ Cl											
- mo				Fmnirical			Found, %				Cal	lculated,	o/o	
ponud	22	Yield, %	Mp, °C (solvent)	formula	υ	H	ฮ	z	s	υ	ш	5	N	ß
	H													
et .	ccoocH ₃	87	173-174	C17H23Cl2NO5S	47,55	5,65	15,20	3,41	7,61	48,11	5,46	16,70	3,30	7,55
	CH2C6H5		(auconor)							<u>.</u>				
	н -													
q	ccu2c,Hs	96	163,5-164	C ₁₆ H ₂₁ Cl ₂ NO ₅ S	47,25	5,19	16, 75	3,02	7,68	46,83	5,15	17,28	3,41	7,81
	COOH		(rama)											
د.	P-CeH4*	00	475-475 5	C.eHerCleNO.S	W 67	5 46	16 58	3.67	7 84	48 73	5 36	17.98	3.55	8.13
)	sulfoxide	<u> </u>	(alcohol)					5			5			

* Is not oxidized further due to insolubility.



The corresponding sulfones (IVa-d) were synthesized by the oxidation of (IIa-d) with hydrogen pero-xide.



EXPERIMENTAL METHOD

<u>Methyl Ester of N-Dimethylacryloyl-DL-phenylalanine (Ia)</u>. To 11.8 g of the acid chloride of dimethylacrylic acid in 150 ml of absolute ether was added in drops, with stirring, in 0.5 h, 35.8 g of the methyl ester of phenylalanine in 50 ml of absolute ether. The reaction mixture was allowed to stand overnight. The hydrochloride of the methyl ester of phenylalanine (V) was filtered, and the filtrate was evaporated in vacuo. The residue was recrystallized; yield 98%.

To 8.6 g of the acid chloride of dimethylacrylic acid in 100 ml of absolute chloroform was added a mixture of 16.5 g of (V) and 14.6 g of $(C_2H_5)_3N$ in 100 ml of absolute CHCl₃, after which the mixture was stirred for 2 h and allowed to stand overnight at ~20°. The solvent was evaporated in vacuo, the residue was dissolved in absolute ether, the triethylamine hydrochloride was filtered, and the ether was evaporated. We obtained (Ia) in 90% yield, mp 47-48° (from a mixture of ether and petroleum ether). Found: C 68.64; H 7.27; N 5.30%. C₁₆H₁₉NO₃. Calculated: C 68.94; H 7.33; N 5.36%.

<u>Amide of N-Dimethylacryloyl-DL-phenylalanine (Ib).</u> (Ia) (6.0 g) was stirred for 2 h with 50 ml of conc. aqueous ammonia that had been additionally saturated with NH₃ at 0°. The precipitate of (Ib) was filtered, dried, and recrystallized from CHCl₃; yield 80%; mp 165-166°. Found: C 67.97; H 7.45; N 11.30%. $C_{14}H_{18}N_2O_2$. Calculated: C 68.27; H 7.36; N 11.37%.

<u>N-Dimethylacryloyl-DL-phenylalanine (Ic)</u>. A mixture of 3.5 g of (Ia) and 0.56 g of NaOH in 25 ml of absolute methanol was allowed to stand overnight. The methanol was evaporated in vacuo, and the residue was dissolved in water, extracted with ether from any possible impurities, and the aqueous layer was acidified with conc. HCl until acid. The precipitate of (Ic) was filtered and washed with water; yield 97%; mp 153-154° (from a mixture of ether and petroleum ether). Found: C 67.63; H 6.92; N 6.00%. $C_{14}H_{17}NO_3$. Calculated: C 67.99; H 6.93; N 5.66%.

<u>Anestheside of Dimethylacrylic Acid (Id).</u> To 5.9 g of the acid chloride of dimethylacrylic acid in 300 ml of absolute ether was added in drops, with stirring, in 1.5 h, 16.5 g of anesthesine in 300 ml of absolute ether. The mixture was allowed to stand overnight. The anesthesine hydrochloride was filtered, the filtrate was evaporated in vacuo, and the precipitate (Id) was recrystallized from CCl₄; yield 95%; mp 126.5-127°. Found: C 67.69; H 6.92; N 5.70%. C₁₄N₁₇NO₃. Calculated C 67.99; H 6.93; N 5.66%.

To 6 g of anesthesine and 5 ml of $(C_2H_5)_3N$ in 100 ml of absolute ether at -3° was added in drops, with stirring, 5.9 g of the acid chloride of dimethylacrylic acid. The mixture was stirred for 1 h at room temperature. The triethylamine hydrochloride was filtered, the filtrate was evaporated in vacuo, and the residue was recrystallized from CCl₄. We obtained a mixture of (Ie) and (III); yield 90%; mp 84-85° (from CCl₄). Found: C 67.22; H 6.94; N 5.73%. C₁₄H₁₇NO₃. Calculated: C 67.99; H 6.93; N 5.66%. NMR parameters: (Id), δ (CH₃)₂C 1.78 and 2.15, δ CH 1.78 ppm; (III), δ _{CH₃} 1.78, δ _{CH₂} = C 4.83, δ _{CH₂}(CO) 3.06 ppm. Treatment of this mixture by the procedure given in [3] gave pure (Ie); yield 89%; mp 152-153° (from CCl₄). Found: C 66.29; H 6.42; N 5.92%. C₁₃H₁₅NO₃. Calculated: C 66.93; H 6.48; N 6.00%.

General Method for the Addition of $ClSCH_2CH_2Cl$ to (Ia-e). To 0.02 mole of (Ia-e) in 30 ml of absolute $CHCl_3$ was added in drops, with stirring, at -8° , 0.02 mole of β -chloroethylsulfenyl chloride in 10 ml of

absolute $CHCl_3$. The reaction mixture was allowed to stand for 1 h at room temperature. The solvent was evaporated in vacuo, and the residue was recrystallized. (IIa-e) were obtained; the yields, melting points, and analysis data are given in Table 1.

<u>General Method for the Preparation of Sulfones (IVa-c)</u>. To 0.005 mole of (IIa, c, d) in 7.5 ml of glacial acetic acid and 1.5 ml of acetic anhydride was added in drops, with cooling in ice water, 2.5 ml of 30% hydrogen peroxide solution and the mixture was allowed to stand for 7 days at room temperature. The solvent was evaporated in vacuo, and the residue was recrystallized. The yields, melting points and analysis data are given in Table 2.

CONCLUSIONS

Compounds of the general formula $\frac{H_3C}{H_3C}$ C(Cl)CH(SCH₂CH₂Cl)CONHR were synthesized for biological testing, from which the corresponding sulfones were obtained by oxidation with hydrogen peroxide.

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